III. Amendments to the Claims

The informality in claim 1 has been corrected by amending claim 1. Additionally, claims 1 and 12 have been amended by adding the phrase "per patient treatment session" so as to clarify the claims. Support for this amendment can be found at at least page 11, lines 11-14 of the specification.

III. The Section 103(a) Rejection

The Office Action rejected claims 1 and 11-15 under 35 U.S.C. section 103(a) as being unpatentable over Ludlow (1992) in view of Simpson (1981) and Jankovic (1991), and stated that res judicata appears to apply to this rejection due to decision 972,367 by the Board of Patent Appeals and Interferences.

Why Res Judicata Does Not Apply

As is well known, the legal doctrine of res judicata does not apply if either: (a) the claims of the present application are patentably different from the claims that were previously adjudicated or; (b) the claims in the present patent application involve a different issue as compared to the claims that were previously adjudicated. See e.g. MPEP 706.03(w)).

The November 28, 2000 decision number 1997-2367 by the Board in parent application serial number 08/075,048 was upon claims all of which were explicitly restricted to use of **type E** botulinum toxin after use of type A botulinum toxin (see page 2 of the Board decision 1997-2367, copy attached).

Contrarily, the claims in the present application are, and have always been, clearly limited to use of **type B** botulinum toxin after use of type A botulinum toxin.

It is clear that type E botulinum toxin is very different from type B botulinum toxin. For example:

1. Type E botulinum toxin and type B botulinum toxin have different intracellular targets or substrates. Thus, the intracellular target for type E botulinum toxin is the SNAP-25 protein, while the intracellular target of the type B botulinum toxin in the VAMP protein. Shone, C., *The mode of action of*

botulinum and tetanus neurotoxins, J Med Microbiol 1994; 41 (1, Suppl):245 (copy attached).

2. The type E and type B toxins have different molecular structures. Thus, the Clostridium botulinum bacterium makes the type E toxin as a single chain molecule, while the type B toxin is made by the bacterium as a mixture of single and dichain molecules. Singh B., et al., *Molecular topography and secondary structure comparisons of botulinum neurotoxin types A, B and E,* Mol Cell Biochem 1989 Mar 16;86(1):87-95, at page 87, right hand column (copy attached). Additionally, as set forth in the paragraph above because the type E and type A toxins have different intracellular targets they must therefore also have different primary, secondary and/or tertiary structures.

3. The type E and type B toxins differ in toxicity. Upon synthesis, the single chain (referred to as "unnicked") type E is much less toxic than is the dichain (referred to as "nicked") type B molecule. *Ibid* at pages 87-88. Thus, the type B toxin is more toxic than is the type E toxin. *Ibid* at page 93, right hand side.

4. The type E and type B toxins differ in the duration of muscular paralysis caused. Thus, the type B toxin has a longer period of activity than does the type E toxin. Dolly, J., et al, *Insights into the extended duration of neuroparalysis by botulinum neurotoxin A relative to the other shorter acting serotypes: differences between motor nerve terminals and cultured neurons*, chapter 8, pages 91-102 of Scientific and Therapeutic Aspects of Botulinum toxin, Brin M., et al editors, Lippincott Williams & Wilkins (2002), (copy attached). See page 92, left hand side column of this publication: "A>>B >F>E".

Hence, the type E and type B botulinum toxins, having different targets, different structures, different toxicities and different durations of effect, are clearly different molecules.

Furthermore, applicants submit attached to this response a copy of the February 8, 2001 of Dr. Mitchell Brin declaration as filed in application 09/490,756 (effective filing date December 28, 1993), now U.S. patent 6,290,961 (use of botulinum toxin type B to treat cervical dystonia). U.S. patent 6,290,961 had the same four applicants as does the present application and has the same assignee. Dr. Brin is the foremost authority on therapeutic use of the botulinum toxins. Paragraph 8 of the Brin declaration states that prior to the December 28, 1993 effective filing date of the invention in application serial number 09/490,756 it would have been "foolhardy and dangerous" to use botulinum toxin type B to treat patients. Clearly if it would have been foolhardy and dangerous as of December 28, 1993 to use botulinum toxin type B to treat patients, it would also have been foolhardy and dangerous as of the June 10, 1993 effective filing date of the present patent application to use type B botulinum toxin to treat patients.

Thus, applicants believe that in light of: (a) the numerous distinctions between type E botulinum toxin and type A botulinum toxin (see above) and; (b) the evidence presented by the Brin declaration, the type B toxin after type A toxin claims in the present patent application are patentably distinct from or involve different issues as compared to the type E botulinum toxin after use of type A botulinum toxin claims which were before the Board in it's decision 1997-2367.

Hence, the doctrine of res judicata does not apply to the claims in the present patent application.

Patentability Over the Combination of Ludlow, Simpson and Jankovic

The Office Action rejected claims 1 and 11-15 under 35 U.S.C. section 103(a) as being unpatentable over Ludlow (1992) in view of Simpson (1981) and Jankovic (1991).

Ludlow discloses use of type F botulinum toxin after type A botulinum toxin. Simpson reviews the structure and activity of the botulinum toxins A-G. Jankovic speculates that botulinum toxins other than the type A botulinum toxin may have utility for patients who no longer respond to type A toxin.

The Combination of Ludlow, Simpson and Jankovic does not render the claims unpatentable because of the evidence presented herein from the co-author of the Jankovic reference which shows that it would have been "foolhardy and dangerous" for a person of ordinary skill at the time of the claimed invention to use botulinum toxin type B in humans. See the attached declaration of Dr. Mitchell Brin.

Dr. Brin is an acknowledged expert in the therapeutic use of botulinum toxin type B (see e.g. the declarant's publications numbers 85 and 86 in Attachment A to the Brin Declaration and paragraph 3 of the Brin declaration).

The Brin declaration provides evidence that:

1. the Jankovic reference discusses use of *only* type A botulinum toxin (Brin Dec. ¶6) (fact statement);

2. as of December 28, 1993 date of the invention in application serial number 09/490,756 it was completely unknown as to whether or not botulinum toxin type B would have any therapeutic efficacy in humans (Brin Dec. ¶6) (fact statement). Clearly, the same conclusion applies to the even earlier (June 10, 1993 effective filing date) filing date of the present patent application.

3. the Jankovic reference does not state that botulinum toxin type B can be used as an alternative or in place of botulinum toxin type A (Brin Dec. ¶7) (fact statement);

4. prior to the December 28, 1993 date of the invention in application serial number 09/490,756 it would have been foolhardy and dangerous to use botulinum toxin type B to treat patients (Brin Dec. ¶8) (expert opinion). Clearly, the same conclusion applies to the even earlier (June 10, 1993 effective filing date) filing date of the present patent application.

5. the Jankovic reference does not teach, suggest, motivate or recommend the use of botulinum toxin type B by physicians to treat patients (Brin Dec. ¶8) (fact statement as to "teach", "suggest" and "recommend", and expert opinion as to "motivate").

The Brin declaration therefore presents significant factual evidence with direct bearing upon the "basic factual inquiries" which must be made in order to make a proper obviousness rejection, which "basic factual inquiries" include the "the scope and content of the prior art". Graham v John Deere, 383 U.S. 1, 148 USPQ 459 at 467 (U.S. Supreme Court 1966) (cited at page 3 of the Office Action). Additionally, even the limited opinion evidence in the Brin declaration is entitled to deference as the opinion of an expert. *In re Alton,* 37 USPQ2d 1578 (Fed Cir. 1996) (copy attached).

An obviousness rejection of the present claims over the combination of the Ludlow, Simpson and Jankovic references must assume that the combination teaches or suggests use of botulinum toxin type B after type A. Thus, the combination of the references must teach or suggest to a person of ordinary skill in the field (i.e. a physician), as of June 10, 1993, that botulinum toxin type B after type A is safe and effective to treat patients – otherwise there would have been no use of the toxin B after toxin A.

In fact, though the evidence shows that is that it would have been "foolhardy and dangerous" to use botulinum toxin type B to treat patients as of the December 28, 1993 filing date in serial number 09/490,756, due to the complete

lack of any clinical experience with the type B toxin (Brin Declaration paragraph 8). Clearly therefore it is logical to conclude that it would have also been foolhardy and dangerous to use type B after type A to treat patients as of the even earlier June 10, 1993 filing date of the present patent application.

Thus, the person of ordinary skill in the art at the time the present invention was made would not have been motivated to use type B toxin after type A because the safety and efficacy of botulinum toxin type B for use on humans for any purpose was completely unknown at the time of the claimed invention.

Hence, it would not have been obvious to one of ordinary skill in the art upon a combination of the teachings of the Ludlow, Simpson and Jankovic references to use type B toxin after type A – indeed it would have been "foolhardy and dangerous."

Decisions from the courts which review patent office decisions are instructive as to the deference and weight to be accorded the evidence presented in the Brin declaration: an expert opinion expressed in a declaration can overcome an obviousness rejection: "The expert opinion were introduced on the issue of the level of ordinary skill...the prima facie case of obviousness has been overcome", and the examiner's obviousness rejection was reversed. *In re Oelrich and Divigard,* 579 F.2d 86, 198 USPQ 210 at 215 (CCPA 1978) (copy attached).

Additionally, *In re May and Eddy,* 574 F.2d, 197 USPQ 601 (CCPA 1978) (copy attached) four declarations were submitted in response to an obviousness rejection. The court relied heavily upon the affidavit from an expert in the field (the Jackson affidavit) which stated that the claimed method of affecting analgesic and morphine antagonistic activity through use of a particular compound "was unexpected and unpredictable" since the property of the compound used in the method to affect analgesic and morphine antagonistic activity "had not previously been established.." (197 USPQ at 606) (emphasis

added). The court concluded based in large part upon the Jackson affidavit (see 197 USPQ 608, paragraph [6]) that the method claims were not obvious, and reversed the examiner's obviousness rejection. *In re May and Eddy* is directly applicable here since the present claims are method claims (treatment of claimed neuromuscular disorders), which use a particular compound (type B toxin after type A toxin).

Hence, the evidence presented by the Brin declaration rebuts the *prima facie* case of obviousness presented by the Office Action and the rejection of the claims should therefore be withdrawn.

B. There Was No Reasonable Expectation of Success Upon Use of Type B Toxin

The assumption in the Office Action is that the art teaches that type B toxin can be used after type A toxin. As of the date of the claimed invention, a person of ordinary skill in the art would not have been motivated by knowledge of the art in the combination of the Ludlow, Simpson and Jankovic references to treat using type B toxin after type A toxin, because the significant differences between the type A toxin and type B toxin would have made it clear to the ordinary person that botulinum toxin type B did not have a reasonable expectation of success as being either safe or effective for the treatment of human patients.

Thus it can be noted that:

A person skilled in the art would have knowledge that while all the botulinum toxins inhibit acetylcholine release at the neuromuscular junction, they do so by affecting different neurosecretory proteins and/or by cleaving these proteins at different sites. For example, it was known around the June 10, 1993 effective filing date of the present patent application that while botulinum toxin type A acts

to cleave the 25 kD synaptosomal associated protein (SNAP-25), botulinum toxin type B acts on vesicle-associated membrane protein (VAMP)[1].

Furthermore, as previously set forth the type E and type B toxins have different molecular structures since the Clostridium botulinum bacterium makes the type E toxin as a single chain molecule, while the type B toxin is made by the bacterium as a mixture of single and dichain molecules.

The Office Action rejected the claims over a combination of the Ludlow, Simpson and Jankovic references. A combination of references does not make a claimed invention obvious unless there is a reasonable expectation of success. *In Re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) (reversing the examiner's determination of obviousness) (copy attached).

It is submitted that a reasonable expectation of success with regard to the use of type B toxin after type A toxin does not exist through a combination of the Ludlow, Simpson and Jankovic references because: (a) none of three combination references disclose or suggests any use of botulinum toxin type B, and; (b) because of the differences and deficiencies, as noted above, in the activities and structures between the various neurotoxins (as explained above).

Upon understanding the known deficiencies between botulinum toxin type A and the type B toxin the logical conclusion is that a combination of the references does not provide either a reasonable expectation of success to achieve the claimed invention or even a predictability of success. With knowledge of the known differences between the type B toxin and the type A toxin, there is nothing in the combination which would led one of ordinary skill in the art, at the time of the claimed invention. to anticipate successful treatment of humans upon administration of type B toxin after type A toxin.

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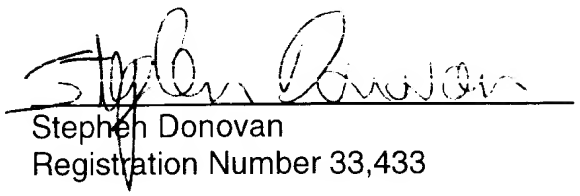
[1] See the previously cited Shone (1994) article.

For these reasons the section 103(a) rejection of the claims should be withdrawn.

V. Conclusion

All issues raised by the Office Action have been addressed. Examination and allowance of claims 1 and 11-15 is requested.

Respectfully Submitted,



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CERTIFICATE OF EXPRESS MAILING UNDER 37 C.F.R. §1.10

I hereby certify that this Transmittal Letter, the response to the Office Action and the documents referred to as enclosed herein are being deposited with the United States Postal Service on February 26, 2003 in an envelope as "Express Mail Post Office To Addressee" mailing label number EL385561228US with sufficient postage for Express Mail addressed to Assistant Commissioner for Patents, Washington, D.C., 20231.

Susan Bartholomew
Name of Person mailing paper

Date: February 26, 2003

Signature of person mailing paper

THE CLAIMS

1. (Currently amended) A method of treating a patient suffering from a neuromuscular disorder or condition wherein the neuromuscular disorder or condition is selected from the group consisting of: disorders of ocular motility; dystonias; tremors; tics; segmental myoclonus; spasms; spasticity; tension headache; levator pelvic syndrome; spina bifida, tardive dyskinesia; Parkinson's disease and; stuttering, the method comprising intramuscular or subcutaneous administration to the patient of up to 1,000 units of a botulinum toxin type A per patient treatment session -until the patient experiences loss of clinical response to the administered botulinum toxin type A, as determined by a failure of the administered botulinum toxin type A to achieve a marked reduction of or to substantially alleviate a symptom of the neuromuscular disorder or condition, and thereafter administering to the patient at least about 80 units of a botulinum toxin type B to thereby again achieve a marked reduction or a substantial alleviation of a symptom of the neuromuscular disorder or condition being treated.

11. (Previously amended) The method of claim 1 , wherein the neuromuscular disorder or condition is cervical dystonia.

12. (Currently amended) A method of treating dystonia in a patient, the method comprising intramuscular or subcutaneous administration to a patient with dystonia of up to 1,000 units of a botulinum toxin type A per patient treatment session until the patient experiences loss of clinical response to the administered botulinum toxin type A, as determined by a failure of the administered botulinum toxin type A to achieve a marked reduction of a symptom of the dystonia, and thereafter administering to the patient at least about 80 units of a botulinum toxin type B.

13. (Previously amended) The method of claim 12, wherein the dystonia is cervical dystonia

14. (Previously added) The method of claim 13, wherein treating the cervical dystonia reduces the severity of an abnormal head position symptom of the cervical dystonia.

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15. (Previously added) The method of claim 13, wherein treating the cervical dystonia reduces a neck pain associated with the cervical dystonia.